REMARKS

In the Office Action mailed 28 August 2002, by Examiner Chakrabarti, in Art Unit 1634, Claims 1-40 are pending and all stand rejected. By the present Response and Amendment, Applicants have cancelled Claims 5, 7, 8 and 10, and amended Claims 1-4, 6, 9, 11-14, 18-19, 22, 24-28, 31-34, and 36-38. Applicants have also added new claims 41-47. No new matter is believed introduced by the present Response and Amendment. Applicants submit that the present amendment clarifies the invention and does not require additional searching by the Examiner. Reconsideration of the Patent Office's rejections is respectfully requested in view of the amendments to the Claims and the accompanying remarks.

I. AMENDMENT OF THE CLAIMS

A. Amended Independent Claim 1

1. *"at least one primer"*

Claim 1 has been amended to replace "primer or primers" with "at least one primer." Basis for this amendment is in Claim 1 as originally drafted.

2. *"wherein at least one of four required types of nucleotides for continuous extension during primer extension reactions is omitted from the non-terminator nucleotide mixture"*

Claim 1 has been amended to replace the language "one or two or three types of non-terminator nucleotides" with "wherein at least one of four required types of nucleotides for continuous extension during primer extension reactions is omitted from the non-terminator nucleotide mixture." In the Specification, the term "non-terminator" is defined as including "a nucleotide base that does not terminate the extension reaction when it is incorporated into the primer extension strand." *Specification, paragraph [0032]*. Further, the Specification states that "at least one of the four required types of nucleotides for continuous extension is left out of the reaction." *Specification, paragraph [0015]*. Thus, there is basis for this amendment and no new matter is presented.

3. *"wherein at least one non-terminator nucleotide is labeled with a detectable marker"*

Claim 1 has been further amended to recite that at least one of the non-terminator nucleotides used in the extension reaction be labeled with a detectable marker. Basis for this

amendment is found in Claim 1 as originally drafted which provided that at least one of the non-terminator nucleotides be *optionally* labeled with a detectable marker.

4. *"performing isometric primer extension by enzymatic or chemical reaction in an appropriate buffer to form isometric primer extension products, wherein the primer extension terminates at a target nucleic acid nucleotide complementary to the omitted non-terminator nucleotide of (c)"*

Claim 1 is further amended to add that isometric extension products are formed by the primer extension reaction. The Specification recites that "a population of equal length (isometric) primer extended nucleic acid [is made] because a definite number of nucleotides is sequence-dependently incorporated." *Specification, paragraph [0016]*. Moreover, "the lack of a free nucleotide in the reaction buffer causes the primer extension to terminate where the missing nucleotide would have been inserted [t]hus, a discrete length of the primer extension product is obtained." *Specification, paragraph [0017]*. Thus, basis exists for this amendment and no new matter is presented.

5. *"with or without a type of terminator nucleotide that is different from the one or two or three types of non-terminator nucleotides"*

Claim 1 has been further amended to delete the limitation of using terminator nucleotides in the extension reaction.

6. *"detecting or quantifying the amount of labeling signal on the isometric primer extension products"*

Claim 1 has been further amended to replace "primer extended nucleotides" with "isometric primer extension products." As stated above, basis for "isometric primer extension products" is found in paragraphs [0016] and [0017] of the specification of the present Application.

7. *"or detecting or quantifying the amount of extended primers by mass spectrometry"*

Claim 1 has been further amended to delete the language "or detecting or quantifying the amount of extended primers by mass spectrometry."

It is respectfully submitted that each of the dependent Claims of the present application (as all dependent Claims depend directly or indirectly from independent Claim 1) now recite the above changes to Claim 1.

B. Amended Dependent Claims

Dependent Claims 2-4, 6, 9, and 11-40 all depend directly or indirectly from independent Claim 1, and therefore, incorporate the limitations of independent Claim 1. Dependent Claims 2-4, 12, 18-19, 24, 27-28, 32-33, and 36-38 have all been further amended for matters of form, thus no new matter is presented. Basis for each of these form amendments exists in the respective claims as originally filed. Claim 6 has been amended to delete the use of terminator nucleotides in the extension reaction. Claim 9 has been amended to depend from Claim 1 instead of Claims 7 or 8 which have been cancelled. Claim 11 has been amended to add that the primer extension products are formed by enzymatic or chemical reaction in an appropriate buffer using a template-dependent enzyme. Basis for this amendment exists in original Claim 1 and original Claim 11. Claim 13 has been amended to depend from Claim 11 instead of Claim 12. Claim 14 has been amended to delete the language "or synthesized non-enzymatically." Claim 22 has been amended to replace "organism" with "mammal." Basis for this amendment exists in original Claim 21. Claims 25 and 26 have been amended to replace "one or more moieties" with "at least one moiety", thus basis for this amendment exists in Claims 25 and 26 as originally filed. Finally, Claims 31 and 34 have been amended to replace "target nucleic acid sequence" with "isometric primer extension products." Basis for this amendment is found in Specification paragraph [0016] of the Application.

C. Newly Added Independent Claims 41, 42 and 43

Applicants have added new independent Claim 41 which recites a method to detect or quantify at least one nucleic acid in a sample, the method comprising the steps of: (a) annealing a primer to the target nucleic acid; (b) extending the primer to form isometric primer extension products incorporating at least one fluorescently labeled nucleotide by omitting at least one of four required types of nucleotides for continuous extension during primer extension reactions; and (c) assaying for incorporation of the fluorescently labeled nucleotide within the isometric extension products. Basis for newly added Claim 41 is found in paragraphs [0008], [0015], [0016], [0017], [0032] and [0034] of the Specification as filed, thus no new matter is presented.

Applicants have also added new independent Claim 42 which further recites a method for detecting or quantifying a target nucleic acid in a sample comprising: (a) preparing at least one primer specifically matched to a predetermined position of the target nucleic acid; (b) annealing the at least one primer from (a) with the target nucleic acid to obtain a primer-nucleic acid duplex at the predetermined position of the target nucleic acid; (c) mixing the primer-nucleic acid duplex from (b) with a non-terminator nucleotide mixture, wherein at least one of four required types of nucleotides for continuous extension during primer extension reactions is omitted from the non-terminator nucleotide mixture; (d) performing isometric primer extension by enzymatic or chemical reaction wherein the primer extension terminates at a target nucleic acid nucleotide complementary to the omitted non-terminator nucleotide of (c); and (e) detecting or quantifying the amount of isometric primer extension products. Basis for newly added Claim 42 is found in original Claim 1 as filed, and paragraphs [0015], [0016], [0017], and [0032] of the Specification as filed, thus no new matter is presented.

Finally, applicants have added new independent Claim 43 which recites a method for detecting or quantifying a target nucleic acid in a sample comprising: (a) annealing at least one primer to a target nucleic acid, wherein the primer is labeled with a detectable marker; (b) extending the labeled primer to form isometric primer extension products by omitting at least one of four required types of nucleotides for continuous extension during primer extension reactions; and (c) detecting the labeled primer extension product. Basis for this amendment exists in original Claim 1 as filed, and paragraphs [0015], [0016], [0017] and [0025] of the specification as filed, thus no new matter is presented.

D. Newly Added Dependent Claims 44, 45, 46, and 47

Applicants have added dependent Claims 44, 45, 46, and 47. Specifically, Applicants have added new dependent Claim 44 which recites that the amount of labeled primer extension products in Claim 42 are detected or quantified by size selection separation and UV absorbance, dye stain, and mass spectrometry methods. Basis for this newly added claim exists in original Claim 10 as filed, and paragraphs [0016], [0037], and [0044]. Applicants have also added new dependent Claim 45 to recite that the target nucleic acid of Claim 1 is synthesized non-enzymatically. Basis for this newly added claim is found in original Claim 14. Applicants have further added new dependent Claim 46 which states that the solid support of Claim 28 is selected

from the group consisting of beads, flat surfaces, chips, capillaries, pins, and wafers. Basis for this newly added claim is found in original Claim 38. Finally, Applicants have added new dependent claim 47 which states that the non-terminator nucleotides may be modified deoxyribonucleotides and ribonucleotides. Basis for this amendment exists in paragraphs [0010] and [0021] of the Specification as filed, thus no new matter is presented.

II. OBJECTION TO CLAIM 38 UNDER 37 C.F.R. 1.75(c)

The Examiner objected to claim 38 as being in improper form because claim 38 is drafted in multiple dependent format and depended on another multiple dependent claim 28 in violation of 37 C.F.R. 1.75(c). Claim 38 has been amended removing its dependency on claim 28. It is respectfully submitted that this amendment obviates this ground for objection.

III. REJECTION OF CLAIMS 27 AND 33 UNDER 35 U.S.C. § 112

The Examiner rejected claims 27 and 33 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. The Examiner contended that the phrase "such as" in claim 27 rendered the claim indefinite because it was unclear whether the limitations following the phrase were part of the invention. The Examiner similarly rejected claim 33 over the phrase "can be". Claims 27 and 33 have been amended to remove the phrases and replace them with clarifying wording. It is respectfully submitted that these amendments obviate this ground of rejection.

IV. REJECTION OF CLAIMS 1-4, 7, 9-16, 18-37, AND 39-40 UNDER 35 U.S.C. § 102(b)

The Examiner rejected claims 1-4, 7, 9-16, 18-37, and 39-40 as anticipated by U.S. Pat. No. 5,965,363 to Monforte et al. (Monforte). The Examiner cited 35 U.S.C. § 102(a) in the Office Action, however, the Examiner rejected the claims under 35 U.S.C. § 102(b). Therefore, for the purposes of the present Response and Amendment, it is assumed that the claims were rejected under 35 U.S.C. § 102(b) as indicated and not under 35 U.S.C. § 102(a).

Concerning independent claim 1, Monforte allegedly discloses a method for detecting or quantifying a target nucleic acid in a sample comprising: a) preparing a primer or primers specifically matched to a predetermined position of the target nucleic acid; b) annealing the primer or primers from a) with the target nucleic acid under high stringency conditions to obtain a primer-nucleic acid duplex at the predetermined position of the target nucleic acid; c) mixing

the primer-nucleic acid duplex from b) with a mixture comprising: (1) one or two or three types of free non-terminator nucleotides and at least one type of non-terminator nucleotide that is optionally labeled with a detectable marker, and (2) with or without a type of terminator nucleotide that is different from the one or two or three types of non-terminator nucleotides in (1); d) performing the primer extension by enzymatic or chemical reaction in an appropriate buffer; and e) detecting or quantifying the amount of labeling signal in the primer extended nucleotides, or f) detecting or quantifying the amount of extended primers by mass spectrometry.

With regard to dependent claims 2-4 and 7, Monforte allegedly discloses an oligodeoxyribonucleic acid primer, a deoxyribonucleic acid of interest, and a deoxyribonucleotide non-terminator nucleotide, wherein at least one of the non-terminator nucleotides is labeled with a detectable marker. Regarding dependent claim 9, Monforte also allegedly discloses that the detectable marker comprises an enzyme or protein moiety, radioactive isotope, a fluorescent moiety or a chemical group. Dependent claim 10 is additionally rejected as anticipated because Monforte allegedly discloses a method, wherein the non-terminator and terminator nucleotides are unlabeled and the detecting or quantifying step is carried out by analyzing the amount of extended primers using mass spectrometry.

With respect to dependent claims 11-13, Monforte allegedly discloses a method, wherein the enzyme is template dependent thermophylic DNA polymerase. Monforte also allegedly discloses that the target nucleic acid is synthesized enzymatically in vitro via polymerase chain reaction as is provided in dependent claims 14-15, 23 and 24, and that the target nucleic acid comprises non-natural nucleotide analogs as is provided in dependent claim 16.

Regarding dependent claims 18-22, Monforte allegedly discloses a method, wherein the target nucleic acid comprises genomic DNA from an organism and that the target nucleic acid can be any sequence including that from a plant, microorganism, bacteria, virus, vertebrate or invertebrate, mammal or human being. Monforte also allegedly discloses that the primer comprises one or more moieties that permit affinity separation of the primer from the unincorporated reagent and/or the nucleic acid of interest as provided in dependent claim 25.

With regard to dependent claims 26-37 and 39-40, Monforte allegedly discloses that the primer or the target nucleic acid sequence can be immobilized onto a solid support. Specifically, Monforte allegedly discloses that the primer comprises one or more moieties that allow

immobilization and that the moieties comprise a special chemical group such as biotin or a DNA sequence that allows the primer to link to a solid support via base pairing to a complementary sequence in the solid support. Monforte also allegedly discloses that immobilization of the primer is reversible by cleaving the primer from the solid support via a chemical, enzymatic, or physical process such as a photocleavable bond. In addition, Monforte allegedly discloses that the primer may be directly synthesized on the solid support by an enzymatic, chemical, or physical method. Finally, Monforte allegedly discloses that the target nucleic acid may be immobilized onto the solid support by hybridization between a complementary capture nucleic acid molecule, which has been previously immobilized to a solid support and a portion of the nucleic acid molecule, which is distinct from the target nucleic acid sequence or that immobilization is accomplished via direct bonding between the solid support and a portion of the nucleic acid molecule, which is distinct from the target nucleic acid sequence.

Applicants respectfully transverse these rejections.

A. Relevant Law

The United States Patent and Trademark Office (USPTO) has the burden of presenting a prima facie case of anticipation. In re Wilder, 429 F.2d 447, 450 (CCPA 1970); In re Spada, 911 F.2d 705, 707-08 (Fed. Cir. 1990). For an anticipation rejection to be appropriate, each and every limitation of the claimed invention must be disclosed in a single prior art reference. In re Paulsen, 30 F.3d 1475, 1478-79 (Fed. Cir. 1994). Every element of the claimed invention must be present in the reference and arranged as in the claim. Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236 (Fed. Cir. 1989).

A claim element that is not expressly set forth in a prior art reference, however, may still anticipate if the element is inherently disclosed by the reference. In re Robertson, 169 F.3d 743, 745 (Fed. Cir. 1999). When anticipation is based on inherency, it must be shown that the undisclosed information was known to be present in the subject matter of the anticipating reference, and that the inherent limitation is necessarily present and not established by "probabilities or possibilities." Elan Pharmaceuticals, Inc. v. Athena Neurosciences, Inc., 304 F.3d 1221, 1228 (Fed. Cir. 2002). The reference must also sufficiently describe the claimed invention to have placed it in possession of a person of ordinary skill in the field of the invention. In re Spada, 911 F.2d 705, 708 (Fed. Cir. 1990).

B. Analysis

1. Pending Independent Claim 1

The Examiner concluded that Monforte discloses "a method for detecting or quantifying a target nucleic acid in a sample comprising: a) preparing a primer or primers specifically matched to a predetermined position of the target nucleic acid; b) annealing the primer or primers from a) with the target nucleic acid under high stringency conditions to obtain a primer-nucleic acid duplex at the predetermined position of the target nucleic acid; c) mixing the primer-nucleic acid duplex from b) with a mixture comprising: (1) one or two or three types of free non-terminator nucleotides and at least one type of non-terminator nucleotide that is optionally labeled with a detectable marker, and (2) with or without a type of terminator nucleotide that is different from the one or two or three types of non-terminator nucleotides in (1); d) performing the primer extension by enzymatic or chemical reaction in an appropriate buffer; and e) detecting or quantifying the amount of labeling signal in the primer extended nucleotides, or f) detecting or quantifying the amount of extended primers by mass spectrometry." Applicants respectfully disagree for the reasons set forth below.

The present invention is distinguishable from Monforte for the following reasons.

(a) Monforte does not disclose using only non-terminator nucleotides in a primer extension reaction while simultaneously leaving out at least one of the available non-terminator nucleotides from the primer extension reaction

Claim 1 has been amended to recite that only non-terminator nucleotides are used in the present invention and that at least one of four required types of nucleotides for continuous extension during primer extension reactions is omitted from the non-terminator nucleotide mixture. Thus, at least one type of available non-terminator nucleotides is left out of the primer extension reaction. The invention in Monforte does *not* disclose using non-terminator nucleotides while simultaneously leaving at least one of the available non-terminator nucleotides out of the primer extension reaction. Instead, Monforte discloses methods for screening nucleic acids for polymorphisms by analyzing amplified target nucleic acids through mass spectrometric techniques via procedures that improve mass resolution and mass accuracy. See Abstract. Specifically, Monforte discloses procedures for modifying the target nucleic acid prior to mass spectrometric analysis. See Col. 4, line 66 to Col. 5, line 7.

For example, Monforte discloses mass modifying the target nucleic acid during the amplification step. See Col. 22, line 65 to Col. 23, line 12 and Example 4. Furthermore, Monforte discloses that "one or more standard deoxynucleoside triphosphates are replaced with modified deoxynucleoside triphosphates." Col. 25, lines 12-14. Thus, Monforte specifically discloses *replacing* a non-terminator nucleotide with a mass modified one, but does not disclose or suggest leaving one of the available non-terminator nucleotides out of the amplification reaction entirely *without* replacing it.

(b) Monforte does not disclose the formation of isometric extension products by omitting at least one free non-terminator nucleotide during a primer extension reaction

Claim 1 has been amended to recite that isometric primer extension products are formed by the primer extension reaction. In the present invention, at least one of four required types of nucleotides for continuous extension during primer extension reactions is omitted from the non-terminator nucleotide mixture during primer extension. Thus, isometric primer extension products are formed during the primer extension reaction due to the omission of one type of the available non-terminator nucleotides, which causes primer extension to terminate where the missing nucleotide would have been inserted. *Specification, paragraphs [0016] and [0017].* Monforte does *not* disclose the formation of isometric primer extension products during primer extension through the omission of an available non-terminator nucleotide. On the contrary, Monforte discloses methods for reducing the size of the nucleic acids to be analyzed via a variety of length reducing techniques *after* primer extension or amplification. See Col. 5, lines 8-28 and Col. 11, lines 15-18. Specifically, Monforte discloses reducing the length of target nucleic acids by any of the known methods that will cleave within one or more flanking regions of the target nucleic acid. See Col. 5, lines 13-16. Although these methods reduce the length of the amplified target nucleic acid, Monforte does not disclose or suggest controlling the length of the primer extension products during primer extension by limiting the types of the available non-terminator nucleotides.

(c) The USPTO has failed to establish a prima facie case that the Monforte reference anticipates independent Claim 1 because Monforte does not disclose each and every claimed limitation in independent Claim 1

The USPTO has the burden of presenting a prima facie case of anticipation. In re Wilder, 429 F.2d 447, 450 (CCPA 1970); In re Spada, 911 F.2d 705, 707-08 (Fed. Cir. 1990). In order for Claim 1 of the present invention to be anticipated by Monforte, each and every limitation of Claim 1 must be disclosed in the Monforte reference. In re Paulsen, 30 F.3d 1475, 1478-79 (Fed. Cir. 1994). Moreover, every element of Claim 1 must be present in the Monforte reference and arranged as in Claim 1 of the present invention. Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236 (Fed. Cir. 1989).

As discussed above, Monforte does not disclose using only non-terminator nucleotides in a primer extension reaction while simultaneously omitting one of four required types of nucleotides for continuous extension during primer extension. Moreover, Monforte does not disclose forming isometric primer extension products through the omission of at least one type of available non-terminator nucleotides. Instead, Monforte discloses substituting at least one of the non-terminator nucleotides with a mass modified one and reducing the length of the nucleic acid to be analyzed by cleaving one or more flanking regions after primer extension or amplification. Therefore, because Monforte does not disclose each and every element of independent Claim 1 as amended, Monforte cannot anticipate Claim 1.

2. Pending Dependent Claims 2-4, 7, 9-16, 18-37, and 39-40

The Examiner rejected dependent claims 2-4, 7, 9-16, 18-37, and 39-40 as anticipated by Monforte for the reasons outlined at the beginning of Section IV above. Applicants have cancelled Claim 7and 10 and amended Claims 2-4, 9, 11-14, 18-19, 22, 24-28, 31-34, and 36-37. A discussion of these amendments is found herein at Section I, sub-section B.

As discussed above, independent Claim 1 cannot be anticipated by the Monforte reference. Because dependent claims necessarily incorporate the claim limitations of the claims from which they depend, and because the pending dependent claims depend either directly from Claim 1 or from other claims that depend from Claim 1, the rejected dependent claims cannot be anticipated in view of the Monforte reference for the same reasons that independent Claim 1 is not anticipated by Monforte.

V. REJECTION OF CLAIMS 5-6, 8 and 17 UNDER 35 U.S.C. § 103(a)

The Examiner rejected claims 5, 6, 8, and 17 under 35 U.S.C. § 103(a) over U.S. Pat. No. 5,965,363 to Monforte et al. (Monforte) in view of Mizusawa et al. (Mizusawa), *Nucleic Acids Research*, (1986), Vol. 14(3), pages 1319-1324.

Concerning dependent Claim 5, the Examiner acknowledged that Monforte fails to teach the use of a terminator nucleotide that is a dideoxyribonucleotide. Mizusawa allegedly teaches a method, wherein the terminator is dideoxyribonucleotide. The Examiner also acknowledged that Monforte fails to teach a combination of non-terminator and terminator nucleotides mix where the mix is dCTP, dGTP, dTTP, and ddATP. Mizusawa allegedly teaches a combination of a non-terminator and terminator nucleotide mix where the mix is dCTP, dGTP, dTTP, and ddATP.

Further, the Examiner acknowledged that Monforte fails to teach that the terminator nucleotide is labeled with or without a detectable marker that is different from the marker labeled with non-terminator nucleotides. Mizusawa allegedly teaches that the terminator nucleotide is labeled with or without a detectable marker that is different from the marker labeled with non-terminator nucleotides. Finally, the Examiner acknowledged that Monforte fails to teach that the non-natural nucleotide analogs comprise 7-deaza-2'-deoxyguanosine. Mizusawa allegedly teaches that the non-natural nucleotide analogs comprise 7-deaza-2'-deoxyguanosine. The Examiner concluded that it would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the method, wherein the non-natural nucleotide analogs comprise 7-deaza-2'-deoxyguanosine of Mizusawa in the method of Monforte.

A. Relevant Law

The USPTO has the burden of showing a prima facie case of obviousness. In re Bell, 991 F.2d 781, 783 (Fed. Cir. 1993). In determining obviousness, the invention must be considered as a whole, and the claims must be considered in their entirety. Medtronic, Inc. v. Cardiac Pacemakers, Inc., 721 F.2d 1563, 1567 (Fed. Cir. 1983). A prima facie case of obviousness is established when the teachings from the prior art itself would have suggested the claimed subject matter to a person of ordinary skill in the art. In re Rhinehart, 531 F.2d 1048, 1051 (CCPA 1976). More specifically, the requirements for establishing a prima facie case of obviousness include: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to

combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations. United States Surgical Corp. v. Ethicon, Inc., 103 F.3d 1554, 1564 (Fed. Cir. 1997).

When a rejection depends on a combination of prior art references, the USPTO must show that there is some teaching, suggestion, or motivation to combine the references. In re Geiger, 815 F.2d 686, 688 (Fed. Cir. 1987). The mere fact that the prior art could be modified would not have made the modification obvious unless the prior art suggested the desirability of the modification. In re Gordon, 733 F.2d 900, 902 (Fed. Cir. 1984). The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. In re Vaeck, 947 F.2d 488 (Fed. Cir. 1991). Finally, obviousness may not be established using hindsight. W.L. Gore & Assocs., Inc. v. Garlock, Inc., 721 F.2d 1540, 1551 (Fed. Cir. 1983).

B. Analysis

1. Pending Dependent Claims 5, 6, 8, and 17

The Examiner rejected claims 5, 6, 8, and 17 under 35 U.S.C. § 103(a) over Monforte in view of Mizusawa. Applicants respectfully traverse the grounds of these rejections for the following reasons. Claims 5 and 8 have been cancelled and Claim 6 has been amended to delete the use of terminator nucleotides. Thus the use of ddATP, or any other dideoxyribonucleotide, in the nucleotide mix (as originally claimed in Claim 6) is no longer part of the claimed invention.

Applicants further respectfully traverse these grounds of rejection in view of the other amended Claims, as it is above-noted that all the pending Claims of the Application have been amended to recite that at least one type of available non-terminator nucleotides is left out of the primer extension reaction. Moreover, all of the pending Claims of the Application have been amended to recite that isomeric primer extension products are formed by omitting at least one type of the available non-terminator nucleotides.

The USPTO has the burden of demonstrating a prima facie case of obviousness. In re Bell, 991 F.2d 781, 783 (Fed. Cir. 1993). When a rejection depends on a combination of prior art references, the USPTO must show that there is some teaching, suggestion, or motivation to combine the references. In re Geiger, 815 F.2d 686, 688 (Fed. Cir. 1987). None of the cited references teach or suggest using only non-terminator nucleotides in an extension reaction while

omitting at least one type of available non-terminator nucleotides from the primer extension reaction. Nor do the cited references teach or suggest forming isometric extension products by such an omission. Therefore, the teachings of Monforte and Mizusawa alone or in combination cannot render the claims obvious. The USPTO has failed to demonstrate a prima facie case of obviousness as the pending Claims define subject matter which is non-obvious and patentably distinct over either the Mizusawa or Monforte references.

CONCLUSION

In light of the foregoing Amendments and Remarks, Applicants believe that the now-pending claims are in condition for allowance. Accordingly, favorable consideration and allowance of the present application is hereby respectfully requested.

PETITION FOR EXTENSION OF TIME

Applicants hereby Petition for a one month extension of time. A check in the amount of $320.00 ($110.00 for extension and $210.00 for extra claims) is enclosed to cover the fee for the same. If any additional fees are in fact due, please charge these fees to deposit account 20-1507.

Respectfully submitted,

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Marked-Up Version of Amended Claims Showing Changes Made

The following is a marked-up version of the amended claims. Deleted text sections are formatted with strikethrough (~~strikethrough~~) and newly inserted text is underlined, and bolded.

1. (amended) A method for detecting or quantifying a target nucleic acid in a sample comprising:

(a) preparing **at least one primer** ~~a primer or primers~~ specifically matched to a predetermined position of the target nucleic acid;

(b) annealing the **at least one** primer ~~or primers~~ from (a) with the target nucleic acid ~~under high stringency conditions~~ to obtain a primer-nucleic acid duplex at the predetermined position of the target nucleic acid;

(c) mixing the primer-nucleic acid duplex from (b) with a **non-terminator nucleotide** mixture, **wherein at least one of four required types of nucleotides for continuous extension during primer extension reactions is omitted from the non-terminator nucleotide mixture, and** ~~comprising: (1) one or two or three types of free non-terminator nucleotides and at least one type of non-terminator nucleotide that is optionally~~ **wherein at least one non-terminator nucleotide is** labeled with a detectable marker, ~~and~~

~~(2) with or without a type of terminator nucleotide that is different from the one or two or three types of non-terminator nucleotides in (1);~~

(d) performing ~~the~~ **isometric** primer extension by enzymatic or chemical reaction in an appropriate buffer **to form isometric primer extension products, wherein the primer extension terminates at a target nucleic acid nucleotide complementary to the omitted non-terminator nucleotide of (c)**; and

(e) detecting or quantifying the amount of labeling signal on the ~~primer-extended nucleotides, or~~ **isometric primer extension products.**

~~(f) detecting or quantifying the amount of extended primers by mass spectrometry.~~

2. (amended) The method according to claim 1, wherein the **at least one** primer is **selected from the group consisting of** a nucleic acid primer, an oligodeoxyribonucleotide, an oligoribonucleotide, ~~or~~ **and** a copolymer of deoxyribonucleic acid and ribonucleic acid.

3. (amended) The method according to claim 1, wherein the target nucleic acid ~~of interest~~ is selected from the group consisting of a deoxyribonucleic acid, a ribonucleic acid ~~or~~, and a copolymer of deoxyribonucleic acid and ribonucleic acid.

4. (amended) The method according to claim 1, wherein the non-terminator nucleotides ~~is~~ are selected from the group consisting of deoxyribonucleotides ~~or~~ and ribonucleotides.

6. (amended) The method according to claim 1, wherein ~~a combination~~ the non-terminator nucleotide mixture ~~of non-terminator and terminator mix is~~ comprises:

~~(a) dATP, dCTP, dGTP, ddTTP or ddUTP,~~

~~(b) dATP, dCTP, dTTP or dUTP, ddGTP,~~

~~(c) dATP, dGTP, dTTP or dUTP, ddGTP,~~

~~(d) dGTP, dGTP, dTTP or dUTP, ddATP,~~

~~(e)~~ (a) dATP, dCTP, dGTP;

~~(f)~~ (b) dATP, dCTP, dTTP or dUTP;

~~(g)~~ (c) dATP, dGTP, dTTP or dUTP; or

~~(h)~~ (d) dCTP, dGTP, dTTP or dUTP.

9. (amended) The method according to claim ~~7 or 8~~ 1, wherein said detectable marker ~~comprises~~ is selected from the group consisting of an enzyme moiety, ~~or~~ protein moiety, radioactive isotope, a fluorescent moiety, ~~or~~ and a chemical group.

11. (amended) The method according to claim 1, wherein ~~said enzyme is template-dependent~~ the primer extension products are formed using a template-dependant enzyme.

12. (amended) The method according to claim 11, wherein the template-dependant enzyme is selected from the group consisting of DNA polymerase, RNA polymerase, ~~or~~ and reverse transcriptase.

13. (amended) The method according to claim ~~12~~ 11, wherein the template-dependant enzyme is *E. coli* DNA polymerase I, a Klenow fragment thereof, T4 DNA polymerase, T7 DNA polymerase, Thermophilic DNA polymerase, retroviral reverse transcriptase, or a combination thereof.

14. (amended) The method according to claim 1, wherein the target nucleic acid is synthesized enzymatically *in vivo*, or *in vitro*, ~~or synthesized non-enzymatically~~.

15. The method according claim 1, wherein the target nucleic acid is synthesized by polymerase chain reaction.

16. The method according claim 1, wherein the target nucleic acid comprises non-natural nucleotide analogs.

17. The method according to claim 16, wherein the non-natural nucleotide analogs comprise deoxyinosine or 7-deaza-2'-deoxyguanosine.

18. (amended) The method according to claim 1, wherein the target nucleic acid ~~comprises~~ is selected from the group consisting of genomic DNA from an organism, RNA transcripts thereof, ~~or~~ and cDNA prepared from RNA transcripts thereof.

19. (amended) The method according to claim 18, wherein the organism is a plant, microorganism, bacteria, or virus.

20. The method according to claim 18, wherein the organism is a vertebrate or invertebrate.

21. The method according to claim 18, wherein the organism is a mammal.

22. (amended) The method according to claim 21, wherein the ~~organism~~ mammal is a human being.

23. The method according to claim 1, wherein an amplification step is performed on the target nucleic acid.

24. (amended) The method according to claim 23, wherein the amplification step comprises an amplification method selected from the group consisting of cloning, transcription, polymerase chain reaction (PCR), ligase chain reaction (LCR), strand displacement amplification (SDA), ~~or~~ and loop mediated isothermal amplification (LAMP).

25. (amended) The method according to claim 1, wherein the primer comprises ~~one or more moieties~~ at least one moiety that permits affinity separation of the primer from the unincorporated reagent ~~and/~~or the nucleic acid of interest.

26. (amended) The method according to claim 1, wherein the primer comprises ~~one or more moieties~~ at least one moiety that allows immobilization of the primer onto a solid support to produce an immobilized primer sequence.

27. (amended) The method according to claim 25 or 26, wherein the ~~moieties~~ at least one moiety comprises a special chemical ~~groups such as~~ selected from the group consisting of biotin ~~or~~ and digitonin.

28. (amended) The method according to claim 25 or 26, wherein the at least one moiety ~~moieties~~ comprises a nucleotide ~~DNA or RNA~~ sequence that allows the primer to link to a solid support, the solid support having a complementary sequence to the nucleotide sequence of the at least one moiety, wherein the primer links to the solid support via base pairing to the a complementary sequence present in the solid support.

29. The method according to claim 1, wherein the primer is directly synthesized on a solid support to produce an immobilized primer sequence.

30. The method according to claim 29, wherein the synthesis is accomplished by enzymatic or chemical or physical method.

31. (amended) The method according to claim 1, wherein the primer is immobilized onto a solid support to produce ~~an~~ immobilized ~~target nucleic acid sequence~~ isometric primer extension products.

32. (amended) The method according to claim 1, wherein the primer is reversibly immobilized ~~on to~~ onto a solid support.

33. (amended) The method according to claim 32, wherein the primer ~~can be cleaved~~ is cleaved from the solid support by a chemical, enzymatic or physical process.

34. (amended) The method according to claim 1, wherein the target nucleic acid is immobilized onto a solid support to produce ~~an~~ immobilized ~~target nucleic acid sequence~~ isometric primer extension products.

35. The method according to claim 1, wherein the target nucleic acid is reversibly immobilized onto a solid support.

36. (amended) The method according to claim 34, wherein the target nucleic acid ~~can be cleaved~~ is cleaved from the solid support by a chemical, enzymatic or physical process.

37. (amended) The method according to claim 31, 32, 34 or 35,, wherein immobilization is accomplished via a photocleavable bond.

38. (amended) The method according to claim 26, ~~28,~~ 29, 31, 32, 34 or 35, wherein the solid support ~~comprises~~ is selected from the group consisting of beads, flat surfaces, chips, capillaries, pins, ~~or~~ and wafers.

39. The method according to claim 31, 32, 34 or 35, wherein said immobilization is accomplished by hybridization between a complementary capture nucleic acid molecule, which has been previously immobilized to a solid support, and a portion of the nucleic acid molecule, which is distinct from the target nucleic acid sequence.

40. The method according to claim 31, 32, 34 or 35, wherein said immobilization is accomplished via direct bonding between the solid support and a portion of the nucleic acid molecule, which is distinct from the target nucleic acid sequence.